

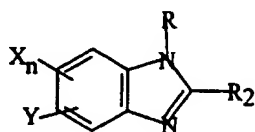


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(21) International Application Number: PCT/US99/11059 (22) International Filing Date: 19 May 1999 (19.05.99) (30) Priority Data: 09/081,384 19 May 1998 (19.05.98) US (71) Applicant (for all designated States except US): THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): CAMDEN, James, Berger [US/US]; 7339 Charter Cup Lane, West Chester, OH 45069 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: COMPOSITIONS FOR THE TREATMENT OF HIV AND OTHER VIRAL INFECTIONS



(I)

(57) Abstract

A pharmaceutical composition that can be used to treat viral infections, particularly HIV. The composition comprises from about 250 mg to about 6000 mg of a benzimidazole derivative of formula (I) or a pharmaceutically acceptable organic or inorganic addition salt thereof, wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl; R is hydrogen or an alkyl group having from 1 to 8 carbon atoms; and R₂ is 4-thiazolyl. The preferred compound is thiabendazole. In the present invention it has been discovered that the compounds described above are useful for the inhibition of HIV and the treatment of HIV infection when used alone or in combination with other anti-viral agents. These compositions can prevent replication of the HIV virus, prevent creation of virus strains that are resistant to treatment with benzimidazoles, prevent or delay infection of cells with HIV virus and delay reappearance of the virus in the treated cells. These compositions are also effective against hepatitis and viruses such as herpes, influenza and rhinoviruses.

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COMPOSITIONS FOR THE TREATMENT OF HIV AND OTHER VIRAL INFECTIONS

TECHNICAL FIELD

This invention is a method of treating viral infections, notably HIV. The pharmaceutical composition contains one or more benzimidazole derivatives, notably a thiabendazole compound.

BACKGROUND OF THE INVENTION

HIV and other viral infections are one leading cause of death. HIV is a disease in which a virus which attacks the body's immune system is replicated in the body. The HIV virus is not easily destroyed nor is there a good mechanism for keeping the host cells from replicating the virus.

Several drugs have been approved for treatment of this devastating disease, including zidovudine (AZT, Retrovir™), didanosine (dideoxyinosine, ddI, Videx™), stavudine (d4T, Zerit™), zalcitabine (dideoxycytosine, ddC, Hivid™), nevirapine (Viramune™), lamivudine (Epivir™, 3TC), protease inhibitors, saquinavir (Invirase™, Fortovase™), ritonavir (Norvir™), nelfinavir (Viracept™), efavirenz (Sustiva™), abacavir (Ziagen™), amprenavir (Agenerase™) indinavir (Crixivan™), ganciclovir, AzDU, delavirdine (Rescriptor™), erythropoietin, colony stimulating factors (G-CSF and GM-CSF), non-nucleoside inhibitors, and nucleoside inhibitors. See M. I. Johnston & D. F. Hoth, Science, 260(5112), 1286-1293 (1993) and D. D. Richman, Science, 272(5270), 1886-1888 (1996). An AIDS vaccine (Salk's vaccine) has been tested and several proteins which are chemokines from CD8 have been discovered to act as HIV suppressors. In addition to the above synthetic nucleoside analogs, proteins, and antibodies, several plants and substances derived from plants have been found to have in vitro anti-HIV activity. However, HIV virus is not easily destroyed nor is there a good mechanism for keeping the host cells from replicating the virus.

Thus, medical professionals continue to search for drugs that can prevent HIV infections, treat HIV carriers to prevent them from progressing to full-blown deadly

AIDS, and treat the AIDS patient. Accordingly, a material which targets the HIV virus and inhibits viral replication is highly desirable.

Herpes simplex is another viral infection which is difficult to cure. Herpes simplex virus (HSV) types 1 and 2 are persistent viruses that commonly infect humans. HSV type 1 causes oral "fever blisters" (recurrent herpes labialis), and HSV type 2 causes genital herpes, which has become a major venereal disease in many parts of the world. No fully satisfactory treatment for genital herpes currently exists. In addition, although it is uncommon, HSV can also cause encephalitis, a life-threatening infection of the brain. (The Merck Manual, Holvey, Ed., 1972; Whitley, Herpes Simplex Viruses, In: Virology, 2nd Ed., Raven Press (1990)). A most serious HSV-caused disorder is dendritic keratitis, an eye infection that produces a branched lesion of the cornea, which can in turn lead to permanent scarring and loss of vision. Ocular infections with HSV are a major cause of blindness.

Hepatitis is a disease of the human liver. It is manifested with inflammation of the liver and is usually caused by viral infections and sometimes by toxic agents. Hepatitis may progress to liver cirrhosis, liver cancer, and eventually death. Several viruses such as hepatitis A, B, C, D, E and G are known to cause various types of viral hepatitis. Among them, HBV and HCV are the most serious. HBV is a DNA virus with a virion size of 42 nm. HCV is a RNA virus with a virion size of 30-60 nm. See D. S. Chen, J. Formos. Med. Assoc., 95(1), 6-12 (1996).

Hepatitis C infects 4 to 5 times the number of people infected with HIV. Hepatitis C is difficult to treat, and it is estimated that there are 500 million people infected with it worldwide (about 15 times those infected with HIV). No effective immunization is currently available, and hepatitis C can only be controlled by other preventive measures such as improvement in hygiene and sanitary conditions and interrupting the route of transmission. At present, the only acceptable treatment for chronic hepatitis C is interferon which requires at least six (6) months of treatment and/or ribavarin which can inhibit viral replication in infected cells and also improve liver function in some people. Treatment with interferon with or without ribavarin, however, has limited long term efficacy with a response rate about 25%.

Hepatitis B virus infection leads to a wide spectrum of liver injury. Moreover, chronic hepatitis B infection has been linked to the subsequent development of hepatocellular carcinoma, a major cause of death. Current prevention of HBV infection is a hepatitis B vaccination which is therapeutically effective. However, vaccination is not effective in treating those already infected (i.e., carriers and patients). Many drugs have been used in treating chronic hepatitis B and none have been proven to be effective, except interferon.

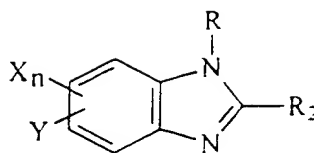
Treatment of HCV and HBV with interferon has limited success and has frequently been associated with adverse side effects such as fatigue, fever, chills, headache, myalgias, arthralgias, mild alopecia, psychiatric effects and associated disorders, autoimmune phenomena and associated disorders and thyroid dysfunction. Because the interferon therapy has limited efficacy and frequent adverse effects, a more effective regimen for the treatment of these viral infections is needed.

Lovett (*Diss. Abstr. Int. (Sci.)* (1979), 39(11), pg. 5315-5316) discloses the use of thiabendazole for the treatment of cancer. Edlind et al. (*Chemical Abstr.* (1994), 121.175012x), Brown et al. (*J. Am. Chem. Soc.* (1961), 83, pg 1764-1765) and Aur (*J. Pediatr.* (1971), 78(1), pg. 129-131) disclose the use of thiabendazole for the treatment of helminthic infections. Wagner et al. (U.S. 3,370,957) disclose antifungal compositions of thiabendazole.

To date, there has been no disclosure or suggestion of the use of thiabendazole for the treatment of viral infections. However, because of the many disadvantages set forth for the treatment of viral infections, there is a continuing need for new and improved methods of treating viral infections.

SUMMARY OF THE INVENTION

A pharmaceutical composition for treatment of animals, and in particular, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount anti-viral compound of the formula I:



(I)

wherein:

X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms;

n is a positive integer of less than 4;

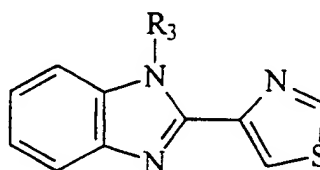
Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl;

R is hydrogen, or an alkyl group of from 1 to 8 carbon atoms; and

R_2 is 4-thiazolyl is claimed.

Preferably the benzimidazole is substituted with either a chloro (Cl^-) or oxychloro (ClO^-) in the 5 or 7 position (meta to the bridging carbons of the benzene ring) and the remaining substituents of the benzene ring are hydrogen.

Preferred compounds are those of the formula III.



(III)

wherein R_3 is hydrogen or an alkyl of 1 through 8 carbon atoms or the non-toxic, pharmaceutically acceptable acid addition salts, thereof, with either organic and inorganic acids. The most preferred compound is 2-(4-thiazolyl)benzimidazole.

The compositions can also be used to treat HIV and other viral infections. The drug can be given daily or from 1 to 4 times a week.

In the present invention it has been discovered that the compounds described above are useful for the inhibition of HIV and the treatment of HIV infection. The present invention also provides methods for the treatment of HIV infection comprising

administering to a host infected with HIV a pharmaceutically or therapeutically effective or acceptable amount of a compound as described above, particularly those wherein R is 4-thiazolyl.

More specifically, this invention provides an anti-viral composition comprising a pharmaceutical carrier and a benzimidazole derivative as defined herein along with a method for treating viral infections. These compositions can prevent replication of a virus, create virus resistance in the patient, prevent or delay infection of cells with a virus, prevent the formation of viruses resistant to treatment with anti-viral agents, increase the life span of cells infected with a virus and/or delay reappearance of a virus in the treated cells.

This invention provides compositions and methods of treating viral infections such as HIV, herpes, hepatitis, influenza and/or rhinoviruses with the anti-viral composition either alone or in conjunction with other treatments.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions:

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

As used herein, the term "therapeutically effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "therapeutically effective amount" will generally vary with such factors as the particular condition being treated, the physical condition of the patient, the type of mammal being treated, the duration of the treatment, the nature of concurrent therapy (if any), the specific formulations employed and the structure of the compounds being used. Therapeutically effective amounts are generally recognized as being safe and effective amounts.

As used herein, a "pharmaceutical addition salt" or "pharmaceutically acceptable salt" is a salt of the anti-viral compound with an organic or inorganic acid. These

preferred acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and others known to those of ordinary skill in the art.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the anti-viral agent to the animal or human. The carrier may be liquid or solid and is selected according to the intended route of administration.

The anti-viral compounds of the invention are the benzimidazoles and/or their salts. The benzimidazoles are described in detail below. The preferred anti-viral compound is the product sold by Merck under the name "thiabendazole".

As used herein, "viruses" includes viruses which infect animals or mammals, including humans. Viruses includes HIV, influenza, polio viruses, hepatitis, herpes, rhinoviruses, and others known to those of ordinary skill in the art.

As used herein, "adjunct therapy" means that the patient in need of the drug is treated or given another drug for the disease in conjunction with the benzimidazole derivatives. This adjunct therapy can be sequential therapy where the patient is treated first with one drug and then the other within a given time period or can be concomitant therapy where the two drugs are administered substantially simultaneously.

B. THE ANTI-VIRAL COMPOUNDS

The anti-viral benzimidazole compounds of the invention are those of the formulae (I) or (II). A preferred compound is 2-(4-thiazolyl)benzimidazole or the non-toxic, pharmaceutically acceptable acid addition salts thereof. Suitable acid addition salts are acid addition salts are organic or inorganic acid addition salts selected from the group consisting of chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates and others known to those of skill in the art.

Prodrugs of the benzimidazole compounds are also provided by the present invention. A "prodrug" is considered to be a compound of the formulae I, II or III having one or more functional groups or carriers covalently bound thereto which functional groups or carriers are removed from the compound of the formulae I, II or III to form the

respective compound. A prodrug of a benzimidazole compound is prepared by modifying one or more functional groups present in the compound with one or more masking groups in such a way that the masking groups are cleaved, either in routine manipulation *ex vivo*, *in vivo*, *in vitro*, or to form the parent compound. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, or benzoate derivatives of alcohol and amine functional groups in the benzimidazole derivatives; phosphate esters, dimethylglycine esters, aminoalkylbenzyl esters, aminoalkyl esters and carboxyalkyl esters of alcohol and phenol functional groups in the benzimidazole derivatives; and others known to those of ordinary skill in the art.

The pharmaceutically acceptable salts of the benzimidazole derivatives include the conventional non-toxic salts or the quaternary ammonium salts of the benzimidazole compounds formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention are synthesized from the benzimidazole derivatives which contain a basic or acidic moiety by conventional chemical methods. Generally, such salts are prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference. The disclosures of all of the references cited herein are hereby incorporated herein by reference in their entirety.

The benzimidazole derivatives are prepared in a number of ways well known to those of ordinary skill in the art of organic synthesis. The benzimidazole derivatives are synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those of ordinary skill in the art. Preferred methods include but are not limited to those methods described below. These compounds are prepared according to the method described in U.S. 3,738,995 issued to Adams et al., June 12, 1973. The thiazolyl derivatives are prepared according to the method described in Brown et al., *J. Am. Chem. Soc.*, 83, 1764 (1961) and Grenda et al., *J. Org. Chem.*, 30, 259 (1965). The disclosure of each of the references cited above is hereby incorporated by reference.

C. DOSAGE AND DOSAGE DELIVERY FORMS

The identity of the anti-viral compound, the pharmaceutical carrier and the amount of compound administered will vary widely depending on the species and body weight of mammal and the virus or viral infection being treated. The dosage administered will vary depending upon known factors, such as the pharmacodynamic characteristics of a specific anti-viral compound and its mode and route of administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment being administered; the frequency of treatment with a compound of the formulae I, II or II; and the desired therapeutic effect.

The benzimidazole is preferably micronized or powdered so that it is more easily dispersed and solubilized by the body. Processes for grinding or pulverizing drugs are well known in the art. For example, a hammer mill or similar milling device are used. The preferred particle size is less than about 100 μ and preferably less than 50 μ .

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 5000 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. Based on the body weight of the patient, the dosage may be administered in one or more doses

several times per day or per week. Multiple dosage units may be required to achieve a therapeutically effective amount. For example, if the dosage form is 1000 mg, and the patient weighs 40 kg, one pill will provide a dose of 25 mg per kg for that patient. It will provide a dose of only 12.5 mg/kg for a 80 kg patient.

The anti-viral compounds of the invention have exhibited efficacy *in vivo* against viruses and cancers in mice at doses of about 500 mg/kg, 2500 mg/kg, 3500 mg/kg, 4000 mg/kg, 5000 mg/kg and 6000 mg/kg. Generally, an effective dose in mice is about 12 times the expected effective dose in humans. By way of general guidance, for humans a dosage of as little as about 30 milligrams (mg) per kilogram (kg) of body weight and up to about 10000 mg per kg of body weight is suitable as a therapeutically effective dose. Preferably, from about 250 mg/kg to about 5000 mg/kg of body weight is used. Other preferred doses range between 100 mg/kg to about 3000 mg/kg of body weight. However, a dosage of between about 2 milligrams (mg) per kilogram (kg) of body weight to about 400 mg per kg of body weight is also suitable for treating some viral infections.

Intravenously, the most preferred rates of administration may range from about 1 to about 1000 mg/kg/minute during a constant rate infusion. Benzimidazole derivatives may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily. The benzimidazole derivatives are given in one or more doses on a daily basis or from one to three times a week.

The anti-viral compounds (active ingredients) of this invention are administered to inhibit virus growth or viral infections by any means that produces contact of the active ingredient with the agent's site of action in the body of a mammal or animal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in combination with other therapeutic agents

A dosage unit may comprise a single compound or mixtures thereof with other compounds, other viral inhibiting compounds or other anti-viral compounds. The benzimidazole derivatives can be administered in oral dosage forms as tablets, capsules,

pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The benzimidazole derivatives may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The compounds herein described in detail form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically acceptable carrier or carrier materials) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a liquid form suitable for oral, rectal, topical, intravenous injection or parenteral administration.

The benzimidazole derivatives can be administered alone but are generally mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of carrier is generally chosen based on the type of administration being used.

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like.

Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like.

Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The benzimidazole derivatives can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and

multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Benzimidazole derivatives may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parentally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as immediate release products or as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

For oral administration in liquid dosage form, the oral drug components are combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage

forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

The benzimidazole derivatives may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittent throughout the dosage regimen.

Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Useful pharmaceutical dosage forms for administration of the compounds of this invention are illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 to 500 milligrams of powdered active ingredient, 5 - 150 milligrams of lactose, 5 -50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 - 500 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 - 500 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 50-275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable solution

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 ml contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 ml of vanillin.

The present invention also includes pharmaceutical kits useful, for example, for the treatment of HIV infection, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a benzimidazole derivative. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Printed instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit. It should be understood that although the specified materials and conditions are important in practicing the invention, unspecified materials and conditions are not

excluded so long as they do not prevent the benefits of the invention from being realized.

D. Adjunct Therapy

One or more benzimidazoles can be used in a single treatment. One or more benzimidazole derivatives can be combined with other antiviral agents or potentiators. Potentiators are materials which affect the body's response to the anti-viral agent. In the case of HIV, an adjunct therapy with AZT, TC-3 or protease inhibitors will generally be effective. In the case of hepatitis, acyclovir, famcyclovir or valacyclovir, Ribavirin, interferon or combinations of Ribavirin and Interferon or beta globulin can be administered as an adjunct therapy. For herpes, a recombinant alpha interferon can be used.

In some embodiments of the invention, thiabendazole is used in combination with one or more other anti-inflammatory, anti-viral, anti-fungal, amoebicidal, trichomonocidal, analgesic, anti-neoplastic, anti-hypertensives, anti-microbial and/or steroid drugs to treat antiviral infections. In some preferred embodiments, viral infections are treated with a combination of thiabendazole with one or more of beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, nitrofurazone, nalidixic acid, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac, acyclovir, amantadine, rimantadine, recombinant soluble CD4 (rsCD4), anti-receptor antibodies (for rhinoviruses), nevirapine, cidofovir (Vistide™), trisodium phosphonoformate (Foscarnet™), famcyclovir, pencyclovir, valacyclovir, nucleic acid/replication inhibitors, interferon, zidovudine (AZT, Retrovir™), didanosine (dideoxyinosine, ddI, Videx™), stavudine (d4T, Zerit™), zalcitabine (dideoxycytosine, ddC, Hivid™), nevirapine (Viramune™), lamivudine (Epivir™, 3TC), protease inhibitors, saquinavir (Invirase™, Fortovase™), ritonavir (Norvir™), nelfinavir (Viracept™), efavirenz (Sustiva™), abacavir (Ziagen™), amprenavir (Agenerase™) indinavir (Crixivan™), ganciclovir, AzDU, delavirdine (Rescriptor™), rifampin, clathromycin, erythropoietin, colony stimulating factors (G-CSF and GM-CSF), non-

nucleoside reverse transcriptase inhibitors, nucleoside inhibitors, adriamycin, fluorouracil, methotrexate, asparaginase and combinations thereof.

When thiabendazole is used in combination with other therapeutic agents, the ratio of thiabendazole to the other therapeutic agent will be varied as needed according to the desired therapeutic effect, the observed side-effects of the combination, or other such considerations known to those of ordinary skill in the medical arts. Generally, the ratio of thiabendazole to other therapeutic agent will range from about 0.5% : 99.5% wt. to about 99.5% : 0.5% wt.

When thiabendazole is administered before or after other therapeutic agents to treat viral infections, the respective doses and the dosing regimen of thiabendazole and the other therapeutic agent may vary. The adjunct therapy can be sequential, that is the treatment with one agent first and then the second agent, or it can be concomitant treatment wherein two or more agents are administered substantially at the same time. The sequential therapy can be within a reasonable time after the completion of the first therapy before beginning the second therapy. The treatment with both agents at the same time can be in the same daily dose or in separate doses. For example treatment with one agent on day 1 and the other on day 2. The exact regimen will depend on the disease being treated, the severity of the infection and the response to the treatment.

For example, a full dosing regimen of thiabendazole can be administered either before or after a full dosing regimen of the other therapeutic agent, or alternating doses of thiabendazole and the other therapeutic agent may be administered. As a further example, thiabendazole can be administered concomitantly with the other therapeutic agent.

E. METHOD OF TREATMENT

The method of treatment can be any suitable method which is effective in the treatment of the particular virus type that is being treated. Treatment may be by oral, rectal, topical, parenteral or intravenous routes of administration and the like. The method of applying an effective amount also varies depending on the virus or viral infection being treated. It is believed that parenteral treatment by intravenous,

subcutaneous, or intramuscular application of the benzimidazole compounds, formulated with an appropriate carrier, additional viral inhibiting compound or compounds or diluent to facilitate application will be the preferred method of administering the compounds to warm blooded animals.

The method of treating viral infections may also be by oral, rectal, topical, parenteral or intravenous administration. The actual time and dosage will depend on the virus being treated and the desired blood levels.

The following examples are illustrative and are not meant to be limiting to the invention. The following examples illustrate the effectiveness of thiabendazole, 2-(4-thiazolyl)-1H-benzimidazole, against HIV and the benzimidazoles derivatives against a number of viruses.

Thiabendazole is effective at totally suppressing HIV virus production in chronically infected cells. The extra cellular viral count goes effectively to zero or non-detectable levels. Thiabendazole does not kill the chronically infected cells even though it reduces the rate of infected cell proliferation at therapeutically effective concentrations. Thiabendazole does not affect CD₄ expression in uninfected cells. At effective concentrations, thiabendazole slows but does not alter the normal cellular RNA or protein synthesis of either infected or non-infected cells. Thiabendazole is effective in a variety of chronically infected cell types (this effect does not appear to be cell type specific.)

Thiabendazole is effective against a variety of HIV virus strains. (Not virus strain specific - although some variance by strain is observed; SK-1>IIIB>RF). Thiabendazole does not appear to be effective on SIV *in vitro* or *in vivo* under the test conditions employed.

After 20 months of agent administration, no virus strains resistant to thiabendazole have developed in tests designed to promote such development. Resistance developed in six months or less in the test employed for existing HIV drugs, with resistance strains for protease inhibitors developing in about 3-4 months.

Thiabendazole does not adversely affect the activity of existing HIV drugs. AZT, 3TC, ddC, ddI or protease inhibitors (saquinavir and indinavir) in acutely infected cells,

nor do any of these existing drugs interfere with the efficacy of thiabendazole in chronically infected cells.

Thiabendazole is also effective against protease inhibitor resistant viruses.

Thiabendazole confers temporary suppression of HIV viral production from 4 to 80 days after treatment stops.

The results of these studies are summarized in detail below:

Example 1

HIV Testing

HIV Virus Replication Study

Thiabendazole was tested in chronically infected HIV virus. These cell populations contain integrated copies of the HIV genome and constitutively produce HIV at relatively high levels (CEM-SK1, U937-SK1 and H9-SK1 from Frederick Research Center, Maryland) or are latently infected and only produce virus after stimulation with phorbol esters, tumor necrosis factor or IL6 (U1 and ACH2). When treated with a compound of the formula II, virus products were reduced in all cell lines tested and the compounds did not stimulate virus production from the latently infected cells. Reductions in virus production were observed when quantifying supernatant reverse transcriptase activity, supernatant p24 as well as intracellular p24, indicating the compounds inhibit virus production at a step of replication prior to production of intracellular proteins.

Quantification of the infectivity of virions produced from the infected cells demonstrates reductions in the number of infectious virions in parallel with reductions in supernatant RT or p24, indicating that the compounds reduce the amount of virus produced, but not the quality of the virions. Inhibition of virus production from the chronically infected cells was observed at concentrations which were nontoxic to the target cells. Thiabendazole inhibited virus production at concentrations great than 1-10 μ g/ml.

Toxicity to the chronically infected cells was similar to that observed with the uninfected cells. Evaluation of thiabendazole on chronically infected cells was performed by evaluation of thymidine (DNA), uridine (RNA) and leucine (protein)

incorporation into cellular macromolecules. Inhibition of cellular macromolecule synthesis paralleled the toxicity of the two compounds as would be expected and did not occur at lower nontoxic concentrations found to inhibit virus production from the chronically infected cells.

After 28 days of treatment with these compounds on chronically infected cells, the toxicity of the compounds to the target cells appeared similar in both uninfected and chronically infected cells. The compounds do not preferentially kill HIV-infected cells. Reductions in the level of virus production were stable and were observed at concentration greater than 10 $\mu\text{g/ml}$ for thiabendazole.

These results suggest that thiabendazole can quickly reduce the level of virus production from cell populations chronically infected with HIV-1 and the antiviral effect is maintained with prolonged compound exposure. This reduction of virus production occurs at concentrations which are substantially nontoxic to the host cell and which have substantially no effect on the synthesis of cellular DNA, RNA and protein.

Virus Resistance Studies

Chronically infected HIV cells were cultured in the presence of thiabendazole at 1 $\mu\text{g/ml}$ for the first month, 5 $\mu\text{g/ml}$ for the second month, 10 $\mu\text{g/ml}$ for the third month, 20 and 40 $\mu\text{g/ml}$ for the fourth month and 80 $\mu\text{g/ml}$ for the fifth and sixth months. At the end of each month, the cells were evaluated for virus production compared to chronically infected cells not treated with the compounds. For each of the six months of treatment experience, no change in the antiviral effect was noticed and the toxicity of remains identical. thiabendazole remained active against HIV, and resistance to thiabendazole was not rapidly achieved via the selection of resistant viruses or adaptation of the cells to prevent compound induced toxicity. Virus production remained totally suppressed from cultures treated with thiabendazole at 40 and 80 $\mu\text{g/ml}$.

Reappearance of Virus Production from Chronically Infected Cells Previously Treated

Chronically infected cells which were treated with a compound of the formula II for prolonged periods were washed free of the compound and cultured to determine if, and when, virus production would resume. Cultures in which treatment resulted in the total elimination of virus production were used in these assays. These cultures included

chronically infected cells cultured in the presence of 20, 40, and 80 $\mu\text{g/ml}$ of thiabendazole. Within 4 days virus production resumed from the cells cultured in the presence of the lower concentrations of each compound (20 $\mu\text{g/ml}$ and 4 $\mu\text{g/ml}$). Virus production resumed by day 12 in the cells cultured at the 40 $\mu\text{g/ml}$ concentration of thiabendazole. For the cells cultured at the highest concentrations of thiabendazole, virus production was first observed at approximately day 70.

Infectability of Cells Treated with Thiabendazole

Cells which were pretreated with thiabendazole for a prolonged period of time were washed free of compound and used as a target cell population. The cells were split into 3 populations and labeled Group 1, 2 or 3. Group 1 was treated with the compound for 24 hours (at the same concentration used in the prolonged treatment phase), washed free of compound and cultured in the presence of infectious virus and fresh compound. Group 2 was pretreated for 24 hours, washed free of compound and cultured in the presence of infectious virus only. Group 3 was cultured for both the pretreatment and the infection phases in fresh medium only (no virus or compound). Virus production from the cell populations was identical irrespective of the culture conditions. These results indicate that the chronically infected cells treated for prolonged periods were not super infected with HIV.

Additional Chronic HIV studies

Chronic HIV-1 infected cells U1 were derived from an acute HIV-1 infection of the promonocytic cell line, U937. The chronic HIV-1 infected cells, ACH-2 were derived from an acute HIV-1 infection of the T cell line, A3.01.

These cells were cultured in medium in the presence of the phorbol ester, PMA. PMA causes the cells (both U1 and ACH-2) to be activated and not divide. It also causes the U-1 cells to differentiate. This results in fewer cells in the PMA-treated cultures than the media alone cultures. Cell viability was measured when these cell lines were treated with the test compound.

Both cell lines constitutively produce a small amount of HIV-1. ACH-2 cell lines tend to produce more HIV-1 than U1 cells as shown by p-24 ELISA. When either cell line is cultured in the presence of PMA, there is an increase in the quantity of HIV-1 produced as measured by the p-24 antigen ELISA. In addition, the number of institute positive HIV mRNA expressing cells per microscopic field is measured. Comparisons can be made from these numbers since the same number of cells were adhered to the glass slides for each drug concentration (approximately 10×10^6 cells/ml).

These cells were treated with test samples. Thiabendazole at 60 μ g/ml suppressed replication in the HIV monocytes by 74% and the T-cell HIV replication was increased by 26%. The positive control was interferon which suppressed HIV monocytes replication by 80%. AZT showed no activity in this model.

2-(Methoxycarbonylamino)benzimidazole suppressed replication in the HIV monocytes by 9% and the T-cell HIV replication was increased by 44%. The positive control was interferon which suppressed HIV monocytes replication by 80% and suppressed T-cell HIV replication by 60%.

Acute HIV Testing

In an *in vitro* acute model for HIV 2-(4-thiazolyl)-1H-benzimidazole inhibited viral replication by 98% at 60 μ g/ml AZT inhibited viral replication by 98% at 1 μ g/ml..

The therapeutic index (TI), the ratio of the toxic dose of drug to efficacious dose of drug for 2-(4-thiazolyl)-1H-benzimidazole is 2.8 versus 12, 500 for AZT.

Example 2

Herpes

~~In an *in vivo* herpes screening test of 2-(4-thiazolyl)-1H-benzimidazole at a dose~~
of 200 mg/kg dose, 10% of the mice survived with a mean death date of 10.4 days; at 100 mg/kg dose 50% of the mice survived with a mean death date of 9.2 days. The positive control was acyclovir at 75 mg/kg dose wherein 60% of the mice survived with a mean death date of 17.2 days.

2-(4-thiazolyl)-1H-benzimidazole was tested in an *in vitro* herpes model and showed no activity.

Example 3

Influenza

2-(4-thiazolyl)-1H-benzimidazole was tested in an *in vitro* influenza model and showed no activity.

In an *in vivo* model for influenza, 2-(4-thiazolyl)-1H-benzimidazole was tested at 200 mg/kg, 67% of the mice survived with a mean death date of 8 days; at 100 mg/kg, 62% survived with a mean death date of 8.7 days. The positive control was amantadine (75 mg/kg) with 100% of the mice surviving for 21 days.

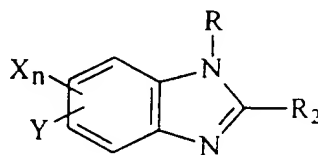
Example 4

Rhinovirus

2-(4-thiazolyl)-1H-benzimidazole benzimidazole was tested in an *in vitro* rhinovirus model and compared to A-36683. The therapeutic index (TI), the ratio of the toxic dose of drug to efficacious dose of drug, for 2-(4-thiazolyl)-1H-benzimidazole is 1-2 versus 1000-3200 for A-36683.

What is claimed is:

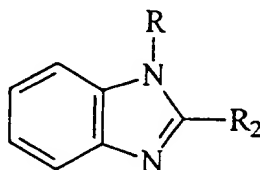
1. A pharmaceutical composition effective for treating viral infections comprising a pharmaceutical carrier and a therapeutically effective amount of a benzimidazole of the formula I:



I

or a pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl; R is hydrogen or an alkyl group having from 1 to 8 carbon atoms; and R₂ is 4-thiazolyl.

2. A pharmaceutical composition according to Claim 1 comprising a pharmaceutically acceptable carrier and from about 25 mg to about 6000 mg of a benzimidazole of the formula II



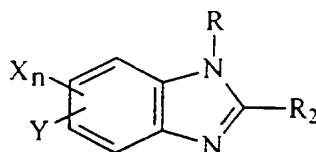
II

or a pharmaceutically acceptable organic or inorganic acid addition salt thereof, wherein R is hydrogen or an alkyl having from 1 to 8 carbon atoms; and R₂ is 4-thiazolyl.

3. A pharmaceutical composition according to Claim 2 wherein said benzimidazole is 2-(4-thiazolyl)benzimidazole present in an amount of about 250 mg to about 5000 mg.

4. A pharmaceutical composition according to Claim 2 wherein said pharmaceutically acceptable salt is an organic or inorganic acid addition salt selected from the group consisting of chloride, bromide, sulfate, nitrate, phosphate, sulfonate, formate, tartrate, maleate, malate, citrate, benzoate, salicylate, ascorbate salts and mixtures thereof.

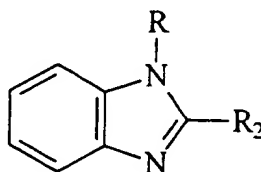
5. A pharmaceutical composition effective for suppressing viral proliferation in a viral infection comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a benzimidazole of the formula I:



I

or a pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl; R is hydrogen or an alkyl group having from 1 to 8 carbon atoms; and R_2 is 4-thiazolyl.

6. A composition according to claim 5 comprising from about 25 mg to about 5000 mg of a benzimidazole of the formula II:

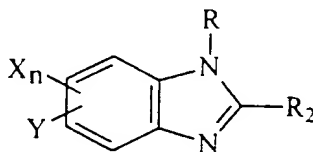


II

or a pharmaceutically acceptable salt thereof, wherein R is hydrogen or alkyl group having from 1 to 8 carbon atoms, and R_2 is 4-thiazolyl.

8. A composition according to claim 7, wherein said benzimidazole is 2-(4-thiazolyl)benzimidazole, or a pharmaceutically acceptable salts thereof and said composition comprises from about 100 mg to about 6000 mg of said benzimidazole.

9. A pharmaceutical composition effective for preventing the development of a virus strain that is resistant to viral infection treatment comprising a pharmaceutical carrier and a therapeutically effective amount of a benzimidazole of the formula I:

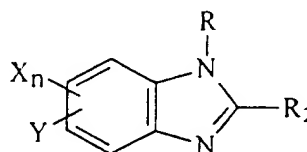


I

or pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl; R is hydrogen or an alkyl group having from 1 to 8 carbon atoms; and R₂ is 4-thiazolyl.

9. A composition according to Claim 8 comprising a pharmaceutically acceptable carrier and from about from about 25 mg to about 5000 mg of said benzimidazole.

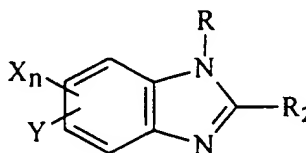
10. A pharmaceutical composition effective for treating a viral infection which is resistant to treatment with a protease inhibitor comprising a pharmaceutical carrier and a therapeutically effective amount of a benzimidazole of the formula I:



I

or pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl; R is hydrogen or an alkyl group having from 1 to 8 carbon atoms; and R₂ is 4-thiazolyl.

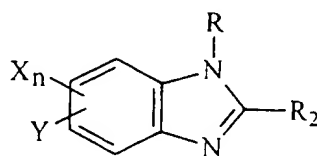
11. A pharmaceutical composition effective for reducing the rate of RNA or protein synthesis in a cell having a viral infection comprising a pharmaceutical carrier and a therapeutically effective amount of a benzimidazole of the formula I:



I

or pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl; R is hydrogen or an alkyl group having from 1 to 8 carbon atoms; and R₂ is 4-thiazolyl.

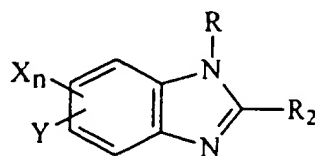
12. A pharmaceutical composition effective for increasing the life span of a mammal having a viral infection comprising a pharmaceutical carrier and a therapeutically effective amount of a benzimidazole of the formula I:



I

- or pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl; R is hydrogen or an alkyl group having from 1 to 8 carbon atoms; and R_2 is 4-thiazolyl.
13. A composition according to claims 1,2,3,4,5,6,7,8,9,10,11, and 12 further comprising an adjunct therapy.
14. A composition according to claim 13, wherein said adjunct therapy is an anti-viral agent.
15. A composition according to claim 13 wherein said adjunct therapy comprises a member selected from the group consisting of acyclovir, amantadine, rimantadine, recombinant soluble CD4 (rsCD4), anti-receptor antibodies, nevirapine, cidofovir, trisodium phosphonoformate, famcyclovir, pencyclovir, valacyclovir, nucleic acid/replication inhibitors, interferon, zidovudine (AZT), didanosine (ddI), stavudine (d4T), zalcitabine (ddC), nevirapine, lamivudine (3TC), protease inhibitors, saquinavir, ritonavir, nelfinavir, efavirenz, abacavir, amprenavir, indinavir, ganciclovir, AzDU, delavirdine, rifampin, clathiromycin, erythropoietin, colony stimulating factors, non-nucleoside reverse transcriptase inhibitors, and nucleoside inhibitors.

16. A composition according to claim 1,2,3,4,5,6,7,8,9,10,11,12,13,14, and 15, wherein the virus infection is caused by one or more of HIV, influenza, hepatitis and rhinovirus.
17. A composition according to claim 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15, and 16, wherein said composition is in an aqueous liquid dosage form selected from the group consisting of a solution, emulsion, suspension solution, and suspension reconstituted from a non-effervescent or effervescent preparation.
18. A composition according to claim 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15, and 16, wherein said composition is in a solid dosage form comprising a carrier selected from the group consisting of lactose, sucrose, gelatin and agar.
19. A method of reducing the rate of RNA or protein synthesis in a cell having a viral infection comprising treating the cell with an effective amount of a benzimidazole of the formula I:



I

or a salt thereof, wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, oxychloro, methyl or ethyl; R is hydrogen or an alkyl group having from 1 to 8 carbon atoms; and R₂ is 4-thiazolyl.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 32107 A (PROCTER & GAMBLE) 17 October 1996 (1996-10-17) abstract page 1, line 6 - line 9 page 2, line 22 - line 25 page 3, line 19 page 4, line 13 - line 22 page 5, line 9 claims 1-5,16 ---	1-19
X	WO 96 40122 A (PROCTER & GAMBLE) 19 December 1996 (1996-12-19) abstract page 1, line 6 - line 8 page 2, line 4 - page 4, line 20 claims 1-10 --- -/--	1-19



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

2 September 1999

Date of mailing of the international search report

16/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Taylor, G.M.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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